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Letter to the editor

Genetic risk variants of schizophrenia associated with left superior temporal gyrus volume

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Schizophrenia is a common and complex psychiatric disease with a high estimated heritability of approximately 80% (Sullivan, Kendler, & Neale, 2003), and hundreds of common single-nucleotide polymorphisms (SNPs) are weakly implicated in the pathogenesis of schizophrenia (Purcell et al., 2009). Gray matter volume (GM) in brain also has an estimated heritability of approximately 60–90% in healthy subjects (Thompson et al., 2001) and reduced GM volumes in patients with schizophrenia have been frequently reported (Chan, Di, McAlonan, & Gong, 2011). A single polygenic

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schizophrenia score (PSS), which was calculated by combining the additive effects of thousands of common independent SNPs weakly associated with schizophrenia explained approximately 3% of the variance in liability for schizophrenia in independent subjects (Purcell et al., 2009). A recent study found that PSS predicts the total brain (TB) and white matter volumes (WM) but not the GM, explaining approximately 5% of the variance in the TB and WM (Terwisscha van Scheltinga et al., 2013). However, it remains unclear whether PSS affects variation in specific GM. Therefore, we investigated the effect of PSS on GM, using (i) voxel-based morphometry (VBM) and (ii) VBM-based region of interest (ROI) methods.

For PSS, the odds ratios for genome-wide SNP data were calculated in a discovery Japanese genome-wide association study (JPN_GWAS) sample including 560 patients with schizophrenia and 548 healthy subjects (Ikeda et al., 2011). On the basis of the genomic-control adjusted *p*-values in an allele-wise association analysis from the discovery sample, nominally associated alleles at the following liberal significance threshold (P_T) were selected: $P_T \leq .1$, $P_T \leq .2$, $P_T \leq .3$, $P_T \leq .4$, and $P_T \leq .5$. Of 67,315 independent SNPs remained after pruning, the numbers of SNPs at each P_T are as follows; $P_T \leq .1$ ($n = 7{,}332$), $P_T \leq .2$ ($n = 14{,}294$), $P_T \leq .3$ ($n = 21{,}205$), $P_T \leq .4$ ($n = 27{,}921$), and $P_T \leq .5$ ($n = 34{,}523$). These data were used to calculate individual PSSs in our target sample of 160 patients with schizophrenia and 378 healthy subjects. The structural images in the target sample were acquired using a 1.5T GE Magnetic Resonance Imaging (MRI) scanner, and the MRI images were processed using the VBM8 toolbox in Statistical Parametric Mapping 8 (SPM8). Detailed information regarding the subjects and methods is provided in the Supplementary Materials and Methods and Table S1. Written informed consent was obtained from all subjects after the procedures had been fully explained. This study was performed in accordance with the World Medical Association's Declaration of Helsinki and was approved by the Research Ethical Committee of Osaka University.

First, to identify brain regions related to PSS based on each threshold, we conducted a whole-brain search in patients with schizophrenia and healthy subjects using a multiple regression model in SPM8. Age, gender and diagnosis were included as covariates. As we found a marginal interaction between diagnosis and PSS on the left superior temporal gyrus (STG), an area of the brain reported to have reduced GM in high-risk individuals and first-episode and chronic schizophrenia patients (Chan et al., 2011) (a maximum of $T = 4.44$ and $P_{FWE} = .075$ at $P_T \leq .5$) (Fig. S1), we next performed separate whole-brain searches to examine the effects of PSS in patients with schizophrenia and healthy subjects. In the patients, PSS was significantly negatively correlated with the local GM in the left STG at the different P_T-values at the whole-brain corrected level ($P_{FWE} < .05$, a maximum of $T = 5.04$ and $P_{FWE} = .012$ at $P_T \leq .3$) (Fig. 1). Higher PSSs were associated with smaller left STG volumes. The STG was the only region showing the association. Such effects were similarly found at the $P_T \leq .2$ ($T = 4.75$, $P_{FWE} = .037$) to $P_T \leq .5$ ($T = 4.73$, $P_{FWE} = .040$) threshold levels, indicating that many more SNPs based on threshold levels more lenient than $P_T \leq .2$ are predictive of

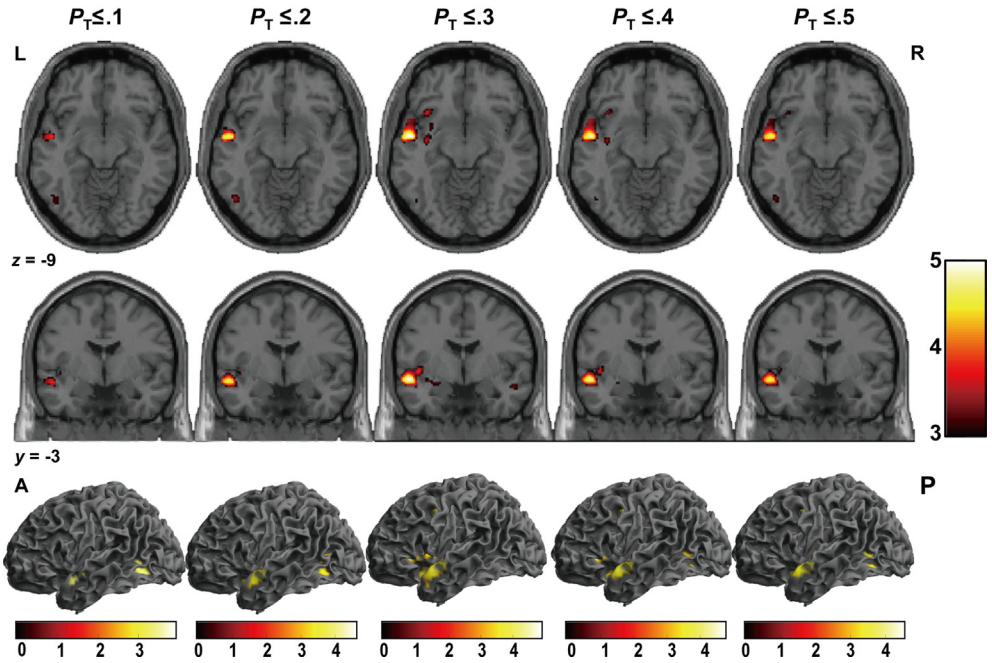

Fig. 1 – Impacts of polygenic scores on gray matter volume in patients with schizophrenia. The effects of PSS based on each threshold ($P_T \leq .1$, $P_T \leq .2$, $P_T \leq .3$, $P_T \leq .4$, and $P_T \leq .5$) on the gray matter volume are shown according to the *t* values showed by the colored bars. The most significant region of PSS association was in the left superior temporal gyrus (Talairach coordinates of peak voxel: −50, −3, −9). The anatomical localizations are displayed on the axial (upper line) and coronal (middle line) sections of a normal MRI spatially normalized to the Montreal Neurological Institute template. *Z* and *y* represent the *z* and *y* coordinates in Talairach space. The surface-rendered view (lower line) of the brain region correlating with PSS is shown. L, left; R, right; A, anterior; P, posterior.

reduced STG volumes. When including the number of nonmissing SNPs, PANSS scores, duration of illness, or antipsychotic dosage as covariates in the VBM analysis, the effects of PSS on the region remained significant ($P_{FWE} < .05$). In contrast, there was no effect of the score on the GM in healthy subjects ($P_{FWE} > .05$).

The STG is involved in auditory processing, the perception of emotions in facial stimuli, and social cognition (Bigler et al., 2007; Radua et al., 2010). To confirm whether the effect at voxel level on the initial VBM analyses is accepted in the larger structural and functional region, we secondly investigated the effects of PSS on calculated total left STG volumes in patients with schizophrenia and healthy subjects using a multiple linear regression model, with the number of nonmissing SNPs as a covariate using PASW18.0 software. Consistent with the VBM results and expected from them, the ROI analysis revealed that the PSS were significantly negatively correlated with the total left STG volume at all different P_T-values (a maximum $R^2 = .032$, $p = .0090$, at $P_T \leq .2$) in the patients (Fig. S2), whereas there was no effect of the score on the region in the controls ($p > .13$). The PSS explained approximately 3.2% of the variance in the total left STG in the patients with schizophrenia, and the effects of PSS on the region reached a peak at $P_T \leq .3$ in the VBM and $P_T \leq .2$ in the ROI analyses. To examine whether there is a strong association of SNPs with the total left STG, we subsequently conducted a GWAS of the region in the same target samples of patients with schizophrenia. We did not observe any association at a widely used benchmark for genome-wide significance ($p > 5.0 \times 10^{-8}$, Figs. S3–S4 and Table S2).

Although Ikeda et al. (2011) reported that there was a significant correlation of the PSSs between the Japanese and UK samples, there are likely many unique risk variants included in the PSS derived in the Japanese dataset. As the genes comprising the PSS in this study are not identical to those in the MRI study of Terwisscha van Scheltinga et al. (2013), we additionally attempted to replicate the association between PSS and TB and WM (Fig. S5). The PSS were marginally negatively correlated with the TB at the $P_T \leq .5$ ($R^2 = .0035$, $p = .049$) and GM at different P_T-values (a maximum $R^2 = .0073$, $p = .015$, at $P_T \leq .5$), whereas there was no effect of the score on the WM ($p > .05$). The reason why we failed to replicate the associations may be caused by false-negative results due to a small number of discovery samples and/or difference of ethnicities between present and previous studies. We used liberal thresholds ($P_T = .1$ to .5) to obtain PSS according to prior studies (Ikeda et al., 2011; Purcell et al., 2009). However, it was more liberal compared to previous study of Terwisscha van Scheltinga et al. (2013) ($P_T = .002$ to .4). The thresholds we used were so liberal as to likely include a large number of false positives.

Substantially larger controls participated in this study. However, there was a lack of the association in the group. As demographic variables in our samples did not match between healthy subjects and patients with schizophrenia, we matched controls to patients for age and sex and additionally performed the VBM analysis, by removing healthy subjects from the total samples. However, the lack of association in the control group did not change. We considered two reasons for the lack of association; 1) The PSS may be related to a genetic architecture of patients with schizophrenia but not controls because the PSS were scores derived from risk of schizophrenia. 2) The association that we detected in patients may result from a false-positive finding due to small samples.

Our findings suggest that a set of SNPs weakly associated with schizophrenia may have an accumulative effect on the brain structure of patients, but not controls. However, our findings should be carefully interpreted because there has not been enough evidence for the heritability of brain structures in unaffected siblings (Birnbaum & Weinberger, 2013). It is interesting to note that the STG is the only brain region showing significant association with the PSS in our schizophrenia dataset, even though structural imaging studies of patients with schizophrenia have identified other brain regions that show volume differences between patients and controls, and that no associations were found in normal subjects, a considerably larger sample. This selective association with the STG and only in the patients was not expected and must be viewed as preliminary pending further replication.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cortex.2014.05.011.

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